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The choice of prodrugs for gene directed enzyme prodrug therapy of cancer.

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Prodrugs are chemicals that are pharmacodynamically and toxicologically inert but which can be converted to highly active species. In cancer chemotherapy, enzyme activated prodrugs have been effective against certain animal tumours. However, in the clinic it has been found that human tumours containing appropriately high levels of the activating enzymes were rare and not associated with any particular type of tumour. Gene directed enzyme prodrug therapy (GDEPT) attempts to overcome this problem by killing tumour cells by the activation of a prodrug after the gene encoding for an activating enzyme has been targeted to the malignant cell. Here we summarise the various enzyme/prodrug systems that have been proposed for cancer therapy and comment on their suitability for GDEPT. This is because systems developed for other applications such as antibody directed enzyme prodrug therapy (ADEPT) may not be suitable for GDEPT. What is required are nontoxic prodrugs that can be converted intracellularly to highly cytotoxic metabolites that are not cell cycle specific in their mechanism of action. The active drugs released should also be readily diffusible and exert a bystander effect. Alkylating agents best meet these criteria. An example of a suitable enzyme/prodrug system may be a bacterial nitroreductase that can convert a relatively nontoxic monofunctional alkylating agent to a difunctional alkylating agent that is some ten thousand times more cytotoxic.

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PMID: 8750009 [PubMed - indexed for MEDLINE]

i686-pc-linux-gnu Jan 21 2003 17:57:06

Prodrugs in cancer chemotherapy.

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At present, chemotherapy is not very effective against common solid cancers, especially once they have metastasized. However, laboratory experiments and studies on dose intensification in humans have indicated that some anticancer agents might be curative, but only if the dose given was very much higher than that attainable clinically. Prodrugs activated by enzymes expressed at a high level in tumors can deliver at least 50-fold the normal dose and can cure animals with tumors normally resistant to chemotherapy. The approach is not practicable clinically because of the rarity of human tumors expressing a high level of an activating enzyme. However, new therapies have been proposed that overcome this limitation of prodrug therapy. Enzymes that activate prodrugs can be directed to human tumor xenografts by conjugating them to tumor-associated antibodies. After allowing for the conjugate to clear from the blood a prodrug is administered which is normally inert, but which is activated by the enzyme delivered to the tumor. This procedure is referred to as ADEPT (antibody-directed enzyme prodrug therapy). Using different combinations of antibody, enzyme and prodrug, many classes of human tumor xenograft have been shown to be very sensitive to this procedure although in most cases they are quite resistant to conventional chemotherapy. Early clinical trials are promising and indicate that ADEPT may become an effective treatment for all solid cancers for which tumor-associated or tumor-specific antibodies are known. Tumors have also been targeted with the genes encoding for prodrug activating enzymes. This approach has been called virus-directed enzyme prodrug therapy (VDEPT) or more generally GDEPT (gene-directed enzyme prodrug therapy) and has shown good results in laboratory systems. These new therapies may finally realize the potential of prodrugs in cancer chemotherapy.

Publication Types:
- Review
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PMID: 8528099 [PubMed - indexed for MEDLINE]

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